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62274 7590 02/13/2008 DARDI & ASSOCIATES, PLLC 220 S. 6TH ST. SUITE 2000, U.S. BANK PLAZA MINNEAPOLIS, MN 55402				
EXAMINER SULLIVAN, DANIEL M				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/758,237

Applicant(s)

HACKETT ET AL.

Examiner

Daniel M. Sullivan

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2007 and 21 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 8, 19-23, 25-28, 31-55, 58-61, 63-67, 69-87, 90-94 and 98-102 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 19-23, 25-28, 31-35, 37, 41-43, 85-87, 90-94 and 102 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-813)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims **withdrawn** from consideration are 5-8,14-17,36,38-40,44-55,58-61,63-67,69-84 and 98-101.

DETAILED ACTION

This Office Action is a reply to the Papers filed 13 February 2007 and 21 May 2007 in response to the Non-Final Office action mailed 7 September 2006. Claims 5-12, 14-18, 36, 38-40, 44-84 and 96-101 were withdrawn from consideration and claims 1-4, 13, 19-35, 37, 41-43, 85-95 and 102 were considered in the 13 February Office Action. Claims 1, 19, 26-28, 41-43, 48, 63, 85 and 93 were amended and claims 2-4, 9-18, 24, 29, 30, 56, 57, 62, 68, 88, 89 and 95-97 were cancelled in the 13 February Paper. Claims 1, 5-8, 19-23, 25-28, 31-55, 58-61, 63-67, 69-87, 90-94 and 98-102 are presently pending.

Election/Restrictions

Applicant's election of Group I, the insulator species DHS5 site of a chicken β -globin locus and the cell species hepatocyte in the reply filed on 16 June 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 44-55, 58-61, 63-67 and 69-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and claims 5-8, 14-17, 36, 38-40 and 98-101 are withdrawn as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the 16 June reply.

As described in the interview summary mailed 14 December 2006, the Examiner agreed that it would be acceptable to amend the generic claim to a single species of insulator element other than the elected species. However, in the response the generic claim was amended to recite

that the transcriptional unit is flanked by at least one CTCF-binding domain, which is still generic to the elected species (i.e., the elected insulator element from the DHS5 site of the chicken β -globin promoter comprises a CTCF-binding domain; see the paragraphs bridging pages 19-20 and 50-51 of the instant specification and references cited therein, which teach that the chicken β -globin loci contains CTCF binding sites). As the claims are still generic to the elected species, the other species will remain withdrawn until such time as the generic claim is deemed allowable or until the generic claim is limited to a single species of invention (e.g., the insulator element comprising SEQ ID NO: 16.)

Claims 1, 19-23, 25-28, 31-35, 37, 41-43, 85-87, 90-94 and 102 are presently under consideration.

Sequence Data

The corrected sequence listing and CRF filed have been entered. However, the submissions filed on 13 February 2007 and 21 May 2007 fail to include "an amendment specifically directing the paper copy of the sequence listing into the application and fails to state that the sequence listing includes no new matter. (See the section under the heading "Applicant Must Provide" in the "Notice to Comply" mailed with the 7 September Office Action. This deficiency might be corrected by filing a statement referring to the 13 February and 21 May submissions and including the required statements.

Response to Amendment and Arguments

Claim Rejections - 35 USC § 101

Rejection of claims 27, 31-35, 37, 41-43, 93 and 95 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is **withdrawn** in view of the amendment of the claims to require that the cell is “isolated”.

Claim Rejections - 35 USC § 112

Rejection of claims 85-87, 91-94 and 102 under 35 U.S.C. 112, second paragraph, as being indefinite is **withdrawn** in view of the amendment of the claims such that they are no longer construed as invoking 35 USC §112, sixth paragraph (i.e., the “means for” language has been removed from the claims).

Rejection of claims 26 and 41-43 under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons set forth in the 7 September Office Action at page 8 is **withdrawn** in view of the claim amendments.

Claim 23 **stands rejected** under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As stated in the 7 September Office Action, claim 23 is indefinite in reciting that the nucleic acid is a member of the group, wherein only a single member is recited (i.e., DNA encoding an mRNA). It appears that Applicant views DNA encoding an mRNA as a Markush group comprised of multiple distinct members; however, it is unclear precisely what defines and

distinguishes the alternative members that make up the group. Applicant's amendments and remarks do not address this ground for rejection.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 19-21, 23, 27, 31-35, 41-43, 85-87, 90-93 and 102 under 35 U.S.C. 102(b) as being anticipated by Chung et al. (1997) US Patent No. 5,610,053 (made of record in the IDS filed 9 July 2004) as evidenced by Pirrotta (1988) *Biotechnology* 10:437-456 and Melcher U. Molecular Genetics, Updated 4 February 2006, <http://opbs.okstate.edu/~melcher/MG/MGW3/MG32217.html>, p. 32217 is **withdrawn** in view of the amendment of the independent claims to require that the transposon comprises at least two inverted repeat sequences that specifically bind to a Sleeping Beauty transposase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1, 19-23, 27, 28, 31-35, 37, 41-43, 85-87, 90-94 and 102 under 35 U.S.C. 103(a) as being unpatentable over Wooddell et al. (effective filing date 15 October 2001) US Pub. No. 2003/0143740 in view of Chung et al. (*supra*) is **withdrawn** in view of the amendment of the independent claims to require that the transposon comprises at least two inverted repeat sequences that specifically bind to a Sleeping Beauty transposase.

Rejection of claims 1, 25 and 26 under 35 U.S.C. 103(a) as being unpatentable over Wooddell et al. (*supra*) in view of Chung et al. (*supra*) as applied to claims 1 and 13 above and further in view of Pope et al. (1997) *Eur. J. Cancer* 33:1005-1016 is **withdrawn** in view of the amendment of the independent claims to require that the transposon comprises at least two inverted repeat sequences that specifically bind to a Sleeping Beauty transposase.

Claims 1, 19-21, 23, 27, 28, 31-35, 37, 41-43, 85-87, 90-94 and 102 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Hackett et al. (1998) WO 98/40510 in view of Chung et al. (*supra*). This rejection is maintained for the reasons set forth in the 7 September Office Action, beginning at page 12, and herein below in the response to Applicant's arguments.

Claims 1, 25 and 26 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Hackett et al. (*supra*) in view of Chung et al. (*supra*) as applied to claim 1 above and further in view of Pope et al. (1997) *Eur. J. Cancer* 33:1005-1016.

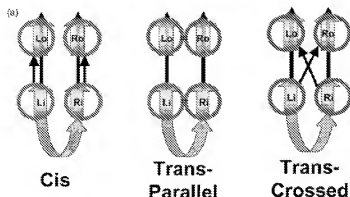
Response to Arguments

In response to the *prima facie* rejection of record, Applicant submits that an artisan would not be motivated to combine Hackett et al. and Chung et al. to achieve the claimed combination of insulator elements with transposons for Sleeping Beauty transposases because the mechanism which insulators flanking a DNA sequence sequester it from outside influences is not known (citing Chung et al., column 22, line 58) and therefore its mechanism of action was unpredictable at the time of filing. Applicant speculates that because leading models of insulator element function all include "looping" of the DNA sequence that is flanked by insulator-binding proteins (citing Chung et al., column 22, line 58 to column 23, line 11) and transposition of Class II DNA transposons such as Sleeping Beauty, also involves a looping mechanism (citing Cui *et al. Journal of Molecular Biology* 318:1221-1235¹) the two looping mechanisms may be in competition. In view of this, Applicant asserts, the artisan would be motivated to seek out a non-looping and non-Sleeping Beauty solution.

Applicant further submits that there is no reasonable expectation of success in the proposed combination because of the unpredictability of: (a) the unknown insulator mechanisms and (b) the unpredictability of two potentially competing looping mechanisms.

¹ It is noted that the Yanagihara et al. reference cited in Applicant's remarks is not of record in the instant application and therefore has not been considered.

These arguments have been fully considered but are not deemed persuasive. As described in the previous Office Action, one would be motivated to modify the transposon taught by Hackett et al. by the inclusion of a chicken β -globin insulator element flanking the transcriptional unit as taught by Chung et al. in view of the teachings of Hackett et al. indicating that the transposons described therein are to be used in the production of transformed cells and transgenic animals and in gene therapy and the teachings of Chung et al. indicating that the inclusion of insulator elements provides a number of advantages in each of the intended uses identified by Hackett et al. Given the clear advantages of including an insulator element recognized in the prior art, the skilled artisan would not be dissuaded from combining the prior art elements based on a lack of absolute knowledge as to the mechanism by which the insulator element works or the possibility that the mechanism of both the insulator element and the transposon involve looping. One of ordinary skill in the field of recombinant DNA routinely combines individual functional elements to obtain combinations exhibiting the collective functions of those elements and, as pointed out in the previous Office Action, Chung et al. demonstrates the effectiveness of the insulator element in various constructs, including a transposon. Furthermore, the proposed mechanisms of the Sleeping Beauty transposon are illustrated in Figure 8 of Cui et al. as follows:



Contrary to Applicant's assertion that the skilled artisan would expect the looping mechanism of an insulator element to interfere with the action of the transposon, one of skill in the art might just as well expect that inclusion of an insulator element that operates via a looping mechanism within the cargo sequence (curved arrow) might actually facilitate the activity of the transposon by bringing the ITRs into closer proximity. The fact is, given the record as a whole, there is no basis for concluding that the mechanism of Sleeping Beauty transposase is incompatible with the insulator element of Chung et al. Furthermore, even if one were to expect some interference, *arguendo*, the level of skill in the art is very high as evidenced by the highly technical nature of the cited publications. Given the high level of skill in the art, one of ordinary skill could readily overcome any interference by routine experimentation (e.g., by determining the optimum positioning of the elements relative to one another). On the whole, notwithstanding the speculative possibility that there might be some routine experimentation involved in optimizing the combination of the prior art elements, one of skill in the relevant art would be motivated to combine the elements given the obvious advantages of including insulator elements with the transposon described by Hackett et al.

With regard to expectation of success, Applicant is reminded that obviousness requires only a reasonable expectation of success. Although some degree of predictability is required, obviousness does not require absolute predictability. (See MPEP 2143.02.) For the reasons stated above, the skilled artisan would have had a reasonable expectation that combining the elements of the prior art would result in a functional transposon comprising insulator elements. It is further noted that the instant application does not include a working example of the claimed combination and provides no guidance at all as to how one of skill in the art might overcome interference of the transposon and insulator elements, which, according to Applicant's remarks, removes any expectation of success in combining the prior art elements. If one were to accept Applicant's assertion that there is no reasonable expectation that the claimed combination of elements would be functional, then one must also conclude that the disclosure has failed to teach the skilled artisan how to make what is claimed in accordance with the requirements of 35 USC § 112, first paragraph². However, given the present record as a whole, one would conclude that combining the prior art elements would require, at most, routine optimization.

With regard to the rejection of claims 1, 25, and 26 as unpatentable over Hackett et al. in view of Chung et al. and in further view of Pope et al. (1997) *Eur. J. Cancer* 33: 1005-1016, Applicant asserts that the claims are not obvious over the art because claim 24, which has been incorporated into amended claims 1 and 85, was not rejected over this combination.

² "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001, 1005.

This argument is not persuasive because, as described in the previous Office Action and herein above, the invention of amended claim 1, as a whole, would have been obvious to one of ordinary skill in the art over the combined teachings of Hackett et al. and Chung et al. Pope et al. is relied upon only for the teaching of a suicide gene and the advantages thereof. Therefore, the invention of the amended claims is still obvious over the cited art for the reasons set forth in the previous Office Action and herein above. It is noted that it was not necessary to reject claim 24 as obvious over Hackett et al. in view of Chung et al. and further in view of Pope et al. in the previous Office Action because the claim was already rejected as obvious over Hackett et al. in view of Chung et al. Therefore, the teachings of Pope et al. were not required to reject claim 24. Thus, to the extent that this rejection might be considered new grounds, it is necessitated by amendment.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC § 103(a) as obvious over the prior art.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim has been amended to recite, "comprising promoter for the suicide sequence nucleic acid that is independent with respect to a promoters the exogenous nucleic acid." The meaning of this phrase is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett et al. (*supra*) in view of Chung et al. (*supra*), as applied to claim 1, and further in view of Wooddell et al. (*supra*).

The instant claim 22 is directed to the transposon of claim 1 wherein the exogenous nucleic acid encodes an antisense RNA or siRNA. As described in the previous Office Action and herein above, the invention of claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Hackett et al. and Chung et al. Hackett et al. and Chung et al. fail to teach an embodiment wherein the exogenous sequence within the transposon encodes an antisense RNA or siRNA. However, Hackett et al. teaches that the transposon system described therein is useful to incorporate therapeutic genes and provide gene therapy to a cell. (See especially the second full paragraph on page 30.)

Wooddell et al. also contemplates the use of a transposon to incorporate therapeutic genes in to the genome of a cell and further teaches that therapeutic genes include those encoding siRNA and antisense molecules. (See especially paragraph 0020.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transposon of Hackett et al. in view of Chung et al. by the inclusion of a nucleic acid encoding an siRNA or antisense RNA as taught by Wooddell et al. In view of the teaching of Hackett et al. that the transposon described therein is useful to deliver a therapeutic gene into a cell, one would clearly be motivated to include any gene that was recognized in the art at the time of invention as a "therapeutic gene" such as the siRNA and antisense taught by Wooddell et al. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the prior art elements because one would expect to be able to incorporate any nucleic acid sequence into the transposon of Hackett et al.

In view of the foregoing, the invention of claim 22, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (<http://pair-direct.uspto.gov>) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636